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(54) Title: METHOD FOR MANUFACTURING A POWDER COMPONENT FOR CEMENT FOR MEDICAL USE, USE OF SUCH POWDER COMPONENT AND SUCH POWDER COMPONENT

(57) Abstract

A method for manufacturing the powder component for a cement for medical use is intended. The cement includes a liquid component containing a polymerizable substance and a powder component containing a plastic substance and an X-ray contrast medium. The liquid component and the powder component are adapted to be mixed for providing a setting mass which is set to form the cement. In order to prevent the formed cement from releasing particles wearing on articulating or bearing surfaces adjacent the point of cementation, a water soluble, non-ionic X-ray contrast medium is mixed with the plastic substance, and for minimizing the risk of damaging the powder component during the sterilisation, sterilising by radiation of the powder component containing said X-ray contrast medium is carried through at a negative pressure and/or in an inert gas atmosphere. Use of the powder component manufactured according to the above in a bone cement is also intended, as is the powder component itself.

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Method for manufacturing a powder component for cement for medical use, use of such powder component and such powder component.

Aseptic loosening in the main longterm complication after a total joint replacement. The osteolysis seen in loosening is caused by, in combination, an increased fluid pressure and an increased inflammatoric response to particles, preferably particles of high density polyethylene (HDPE). Another contributing main factor to loosening is related to the prosthetic stability within bone cement or between the cement and bone tissue.

Contrast agents such as barium sulphate ($BaSO_4$) and zirconium dioxide (ZrO_2) have been added to cement for medical use to achieve radiographic visibility, i.e. visibility to radiophotography, in order to check the operation result.

In order to improve the interface of cement for medical use, various substances such as e.g. hydroxyapatite and growth factors have been added to the cement. Hydroxyapatite has, inter alia, been used in compositions intended for reduction of the wear caused by fragmentation of the cement, whereby particles of the cement enter the joint cavity, i.e. the implant articulation.

There are today clear evidence of that agents impermeable to X-ray emission, i.e. radio opaque agents, which are harder than the metallic counterpart, may cause damages to the articulating surfaces, whereby the wear of the polyethylense increases markedly. In the vast majority of total joint replacement, one of the articulating or bearing surfaces consists namely of a hard, very smooth metallic or ceramic surface, while the other bearing surface is manufactured from high-molecular weight polyethylene. This polyethylene is used as a concave bearing surface. It has been shown that if the radiographic or X-ray contrast media are removed from the bone cement, wear will be reduced. Thus, it is of utmost importance

either to abandon said X-ray contrast media, which is disliked by most surgeons, or to find an X-ray contrast medium which will not affect the strength to a greater extent than in existing cements for medical use, but will be less abrasive when fragmented (released) from the cement.

This is possible by using new types of X-ray contrast media, so called non-ionic contrast media. Radiographic or X-ray contrast media of different types with high osmolality and low osmolality are known today. These contrast media have a high affinity for absorbing water and are in fact water soluble. Preliminary experiments regarding the possibility of mixing these X-ray contrast media into bone cement have been carried through in a laboratory and shows that this is possible and that good radiographic visibility, or visibility to radiophotography, is achieved. Studies are also carried through with bone cell cultures in order to study local toxicity. Existing studies show that non-ionic X-ray contrast media, without being added to bone cement, have very low toxicity especially when contrast media having low osmolality are used.

The sterilisation procedure is of utmost importance for the production of a new cement for medical use. With the non-ionic, water soluble, radiography or X-ray contrast medium, gas sterilisation will induce formation of lumps in the bone cement and sterilisation by radiation will be necessary. There is however, a clear influence by the sterilisation upon a range of cement properties The tensile strength decreases in proportion to the dosage of gamma and beta radiation for the sterilisation. The fatigue resistance will also be significantly reduced. Rheology measurements show a large decrease in viscosity and a delay of the setting time after radiation. This effect on acrylic cement by oxidative degradation has been shown to occur also in other polymers, or plastic substances, such a HDPE. If radiation is carried through

in air, this will cause extensive oxidation and property deterioration in HDPE. This effect increases with time due to ageing of the material. It has been shown that if radiation is carried through at a negative pressure and/ /or by means of a protective inert gas, the dominant effect of the radiation will be cross-linking, not degradation. The effect is further improved if the plastic product after sterilisation by radiation is subjected to a heat treatment in an environment free of oxygen. Sterilisation at a negative pressure and at low temperature also provide improved properties to the polymer.

The object of the present invention is consequently to provide a method for manufacturing the powder component for a cement for medical use in order to prevent the cement obtained from releasing particles which contribute to the wear of articulating or bearing surfaces adjacent the point of cementation as well as minimize the risk of damaging the powder component during sterilisation thereof.

This is arrived at according to the invention by the combination that a water soluble non-ionic X-ray contrast medium is mixed with the plastic substance, whereby particles of the X-ray contrast medium released from the cement after the cementation are dissolved and do not thereby contribute to the wear of articulating or bearing surfaces adjacent the point of cementation, and that sterilisation by radiation of the powder component containing said X-ray contrast medium is carried through at a negative pressure and/or in an inert gas atmosphere in order to minimize the risk of damaging the powder component during the sterilization thereof. The invention also include eventual heat treatment of the powder mixture in the oxygen-free atmosphere after the radiation treatment.

The object of the present invention is also to render it possible to use the powder component manufactured by said method in a cement which is used as bone cement.

A further object of the invention is to provide a powder component which is manufactured in accordance with the abovementioned method.

Below, a method of manufacturing the powder component for a cement for medical use is described. Said cement includes a liquid component containing a polymerisable substance and a powder component containing a plastic substance and an X-ray contrast medium. The liquid and powder components are adapted to be mixed and thereby provide a setting mass which is set to form the cement. A water soluble, non-ionic X-ray contrast medium is mixed with the plastic substance, whereby particles of the X-ray contrast medium released from the cement after cementation are dissolved and do not thereby contribute to the wear of articulating or bearing surfaces adjacent the point of cementation.

Sterilisation by radiation of the powder component containing said X-ray contrast medium is carried through at a negative pressure and/or in an inert gas atmosphere for minimizing the risk of damaging the powder component during the sterilisation.

The water soluble non-ionic X-ray contrast medium which is mixed into the powder component is chosen preferably from the group consisting of iohexol, ioversol, iopamidol, iotrolane and iodixanol and has preferably low osmolality. Other X-ray contrast media which can be used are metrizamide, iodecimol, ioglucol, ioglucamide, ioglunide, iogulamide, iomeprol, iopentol, iopromide, iosarcol, iosimide, iotasul, ioxilane, iofratol and iodecol. Mixtures of said media can also be used.

In the following seven examples, various methods for producing said powder components are described:

Example 1

A non-ionic crystalline contrast medium, e.g. iohexol, is ground to a powder with a particle diameter of about 5 µm. The powder is then mixed with the plastic substance (polymer) in the powder component to an acrylic cement

for medical use, e.g. bone cement, consisting of acrylic polymer particles, preferably polymethylmethacrylate and/or copolymers containing polymethylmethacrylate, with a particle size around 80-100 µm and a very small amount (about 0,5 percent by weight) of a so called initiator substance, e.g. benzoyl peroxide. The X-ray contrast medium comprises preferably about 17-23 percent by weight of the finished powder component (2-3 parts of contrast medium are mixed with 10 parts of the polymer). Other additives can also be added to said powder component. The powder component is then packed up in bag-type portion packs or solid plastic containers, which in both cases are sealed with an air-permeable material, e.g. paper or plastic. The portion packs are placed one by one or in pairs in a further air-permeable bag or container which shall serve as a sterile barrier after sterilisation. Prior to sterilisation, these packs are placed in an air-proof container, the air is removed such that a negative pressure is generated, corresponding to an air pressure of 5 %, preferably about 2,5 %, of the atmospheric pressure. Furthermore, or as an alternative thereto, the container may be filled with an inert gas, e.g. argon, and sealed. The content of oxygen in the air-proof container should then be less than 1 %, preferably less than 0,5 %, of the atmospheric pressure, i.e. the amount of oxygen in the inert gas atmosphere corresponds to a partial pressure of 10 mbar at the most, preferably less than 5 mbar. Sterilisation of the powder component is now carried through by radiation, preferably beta or gamma radiation, with a dose of between 0,5 and 7 Mrad, preferably about 2,5 Mrad. After the sterilisation by radiation and at said negative pressure/inert gas atmosphere, the powder component may preferably be heated to a temperature of 50 - 120°C for 1 min. - 24 hours. After the sterilisation by radiation, the powder bags should preferably, but not necessarily, be kept in the oxygen-free atmosphere until the cement shall be used.

Example 2

As example 1, but where the amount of contrast medium in the powder component is within a range determined by a weight ratio between the contrast medium and polymer of 0,08 : 1 to 0,6 : 1 or such that the powder component contains between about 5 and about 40 percent by weight of X-ray contrast medium.

Example 3

As examples 1-2, but the particle diameter of the non-ionic contrast medium is within a range of 1-50 µm and of the acrylic polymer particles within a range of 20 - 200 µm, with the limitation however, that the diameter of the polymer particles is at least four times the diameter of the contrast medium particles.

Example 4

As examples 1-3, where a powder of an antibiotic substance is added to the powder component before the sterilisation.

Example 5

As examples 1-4 with addition of a colouring substance, e.g. chlorophyll, to the powder component.

Example 6

As examples 1-5, but where the powder component is heated to about 80°C for one hour after the sterilisation by radiation, still packed in an oxygen-free environment.

Example 7

As examples 1-5 except that the powder component is packed directly in a cement mixing container, sealed by means of an air-permeable diaphragm. The cement mixing container filled with powder is packed in an air-permeable pack serving as a sterile barrier. This pack is then placed in an air-proof container, from which the oxygen in the air is evacuated, and sterilisation as in example 1 is carried through.

The powder component manufactured according to the above methods may suitably be used in a bone cement for

fixing prostheses or parts of prostheses, but may also be used in cements for other medical purposes.

The powder components produced in accordance with the above examples thus contains a non-ionic X-ray contrast medium and it is sterilised at a negative pressure and/or in an inert gas atmosphere.

In the above methods, the inert gas atmosphere may, except for argon, consist of helium, neon or nitrogen or mixtures thereof.

Claims:

1. Method for manufacturing the powder component for a cement for medical use,

said cement including a liquid component containing a polymerizable substance and a powder component containing a plastic substance and an X-ray contrast medium, and

wherein the liquid component and the powder component are adapted to be mixed for providing a setting mass which is set to form the cement,

c h a r a c t e r i z e d b y

mixing a water soluble, non-ionic X-ray contrast medium with the plastic substance, whereby particles of said X-ray contrast medium released from the cement after cementation are dissolved and do not thereby contribute to the wear of articulating or bearing surfaces adjacent the point of cementation, and

sterilising by radiation the powder component containing said X-ray contrast medium at a negative pressure and/or in an inert gas atmosphere for minimizing the risk of damaging the powder component during the sterilisation.

2. Method according to claim 1, c h a r a c t e r i z e d b y selecting the water soluble, non-ionic X-ray contrast medium mixed into the powder component from the group consisting of iohexol, ioversol, iopamidol, iotrolane, iodixanol, metrizamide, iodecimol, ioglucol, ioglucamide, ioglunide, iogulamide, iomeprol, iopentol, iopromide, iosarcol, iosimide, iotasul, ioxilane, iofratol and iodecol or mixtures thereof.

3. Method according to claim 1 or 2, c h a r a c t e r i z e d b y the water soluble, non-ionic X-ray contrast medium having low osmolality.

4. Method according to any of claims 1-3, c h a r a c t e r i z e d b y bringing the powder component to contain maximum 40 % by weight of water soluble, non-ionic X-ray contrast medium.

5. Method according to claim 4, c h a r a c t e r i z e d b y bringing the powder component to contain between 5 and 40 % by weight of water soluble, non--ionic X-ray contrast medium.

6. Method according to claim 4 or 5, c h a r a c t e r i z e d b y bringing the powder component to contain between 17 and 23 % by weight of water soluble, non-ionic X-ray contrast medium.

7. Method according to any of claims 1-6, c h a r a c t e r i z e d b y bringing the water soluble, non-ionic X-ray contrast medium to have a particle diameter of maximum 25 % of the particle diameter of the plastic substance.

8. Method according to claim 7, c h a r a c t e r i z e d b y bringing the water soluble, non-ionic X-ray contrast medium to have a particle diameter of between 1 and 50 µm, while the particle diameter of the plastic substance is between 20 and 200 µm.

9. Method according to claim 7 or 8, c h a r a c t e r i z e d b y bringing the water soluble, non-ionic X-ray contrast medium to have a particle diameter of about 5 µm, while the particle diameter of the plastic substance is between 80 and 100 µm.

10. Method according to any of claims 1-9, c h a r a c t e r i z e d b y carrying through the sterilisation by radiation by means of beta or gamma radiation and with a radiation dose of between 0,5 and 7 Mrad.

11. Method according to any of claims 1-10, c h a r a c t e r i z e d b y carrying through the sterilisation by radiation at a negative pressure corresponding to an absolute air pressure of 5 % at the most, preferably about 2,5 %, of the atmospheric pressure.

12. Method according to any of claims 1-11, c h a r a c t e r i z e d b y carrying through the sterilisation by radiation at a negative pressure and at low temperature, preferably about 77°K.

13. Method according to any of claims 1-12, c h a -

racterized by carrying through the sterilisation by radiation in an inert gas atmosphere, said inert gas atmosphere consisting of argon, helium, neon or nitrogen.

14. Method according to any of claims 1-13, characterized by carrying through the sterilisation by radiation in an inert gas atmosphere in which the amount of oxygen corresponds to a partial pressure of 10 mbar at the most, preferably less than 5 mbar.

15. Method according to any of claims 1-14, characterized by heating the powder component to 50 - 120°C for 1 min. - 24 hours after sterilisation by radiation and at a negative pressure and/or an inert atmosphere.

16. Method according to any of claims 1-15, characterized by selecting as plastic substance in the powder component acrylic polymer particles, preferably polymethylmethacrylate and/or copolymers containing polymethylmethacrylate.

17. Method according to any of claims 1-16, characterized by adding a substance initiating polymerization, e.g. benzoyl peroxide, to the powder component before the sterilisation by radiation.

18. Method according to any of claims 1-17, characterized by adding an antibiotic substance to the powder component before the sterilisation by radiation.

19. Method according to any of claims 1-18, characterized by adding a coburing substance, e.g. chlorophyll, to the powder component before the sterilisation by radiation.

20. Method according to any of claims 1-19,
characterized by
placing the powder component in an air-permeable container,

placing in turn the air-permeable container in an air-proof container,

evacuating air from the air-proof container, and

sterilising by radiation the powder component in the air-permeable container.

21. Method according to claim 20, c h a r a c t e r i z e d b y locating the powder component in a bone cement mixing container.

22. Use of a powder component obtained by the method according to any of claims 1-21 in a bone cement for fixing prostheses or parts of prostheses.

23. Powder component for cement for medical use, c h a r a c t e r i z e d i n

that it contains a water soluble, non-ionic X-ray contrast medium, and

that it is sterilised at a negative pressure and/or in an inert gas atmosphere.

24. Powder component according to claim 23, c h a r a c t e r i z e d i n that the water soluble, non-ionic X-ray contrast medium which is mixed into the powder component is selected from the group consisting of iohexol, ioversol, iopamidol, iotrolane, iodixanol, metrizamide, iodecimol, ioglucol, ioglucamide, ioglunide, iogulamide, iomeprol, iopentol, iopromide, iosarcol, iosimide, iotasul, ioxilane, iofratol and iodecol or mixtures thereof.

25. Powder component according to claim 23 or 24, c h a r a c t e r i z e d i n that it contains maximum 40 % by weight of water soluble, non-ionic X-ray contrast medium.

26. Powder component according to any of claims 23-25, c h a r a c t e r i z e d i n that it contains between 5 and 40 % by weight of water soluble, non-ionic X-ray contrast medium.

27. Powder component according to any of claims 23-26, c h a r a c t e r i z e d i n that the powder component contains between 17 and 23 % by weight of water soluble, non-ionic X-ray contrast medium.

28. Powder component according to any of claims 23-27,

c h a r a c t e r i z e d i n that the water soluble, non-ionic X-ray contrast medium has a particle diameter of maximum 25 % of the particle diameter of the plastic substance.

29. Powder component according to any of claims 23-28, c h a r a c t e r i z e d i n that the water soluble, non-ionic X-ray contrast medium has a particle diameter of between 1 and 50 µm, while the particle diameter of the plastic substance is between 20 and 200 µm.

30. Powder component according to any of claims 23-29, c h a r a c t e r i z e d i n that the water soluble, non-ionic X-ray contrast medium has a particle diameter of about 5 µm, while the particle diameter of the plastic substance is between 80 and 100 µm.

31. Powder component according to any of claims 23-30, c h a r a c t e r i z e d i n that it contains an antibiotic substance.

32. Powder component according to any of claims 23-31, c h a r a c t e r i z e d i n that it contains a cobu-ring substance, e.g. chlorophyll.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 25/00, A61L 2/08, A61L 2/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0639382 A1 (MIT PHARMACA AB), 22 February 1995 (22.02.95) --	1-32
A	EP 0676212 A1 (BRISTOL-MYERS SQUIBB COMPANY), 11 October 1995 (11.10.95) --	1-32
A	EP 0701824 A2 (MERCK PATENT GMBH), 20 March 1996 (20.03.96) --	1-32
A	EP 0705609 A2 (MERCK PATENT GMBH), 10 April 1996 (10.04.96) -- --------	1-32

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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